PATENT Case 5400/2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	
S. BERTENSHAW ET AL	GROUP ART UNIT: 120
SERIAL NO.: 08/425,022	EXAMINER: DENTZ
FILED: April 19, 1995	DATE: April 3, 1997

TITLE: SUBSTITUTED FURANS AND FURANONES FOR THE TREATMENT OF INFLAMMATION

DECLARATION UNDER 37 C.F.R. §1.132

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Victor Snieckus, Ph.D., declare that:

1. I received a Bachelor of Science Degree in Chemistry from the University of Alberta in 1959; a Master of Science Degree from the University of California-Berkeley in 1961, and a Ph.D. in Chemistry from the University of Oregon, in 1965;

2. Since 1967, I have been employed as a faculty member of the Department of Chemistry at the University of Waterloo, Waterloo, Ontario, Canada. Currently I hold the position of professor of Chemistry and I direct scientists carrying out research in organic chemistry synthetic methodology;

3. I am the principal author or co-author of approximately 180 publications, with several publications on organic chemistry synthesis methods, including methods and strategies of heteroaromatic metalation;

4. In my professional capacities, I closely and carefully follow the scientific literature regarding organic chemistry and specifically synthetic methods;

5. As a professor of chemistry at the University of Waterloo and an invited lecturer at universities and companies throughout the world, I am aware of what constitutes ordinary skill and knowledge in the art of heterocyclic chemistry, including as it relates to tautomers. In this art it is well known and accepted that:

a. carbonyl-enol tautomerism exists where an enol (vinyl alcohol) form exists in equilibrium with one or more carbonyl forms;

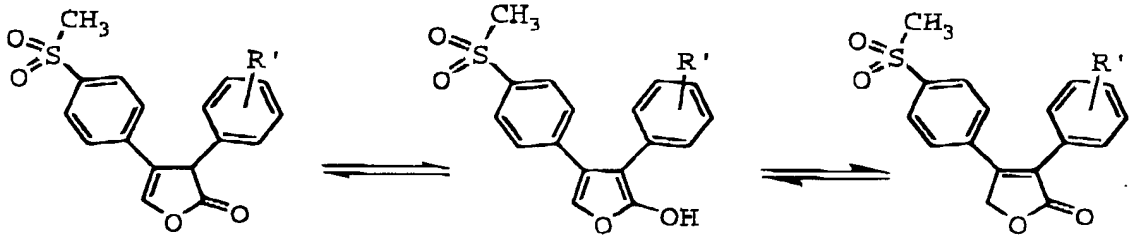
b. the carbonyl-enol tautomeric forms are interconvertable by transfer of a proton;

c. although one tautomeric form may predominate, in solution phase the carbonyl-enol tautomeric forms co-exist;

d. the carbonyl-enol tautomeric equilibrium is greatly affected by phase, solvent, concentration, pH, temperature and the presence of substituents (including those producing inductive, resonance, hydrogen bond-stabilizing or steric effects); and

e. a depiction of one carbonyl-enol tautomeric form embodies all carbonyl-enol tautomeric forms;

6. The structures shown below are tautomers of each other



carbonyl enol carbonyl

7. I have reviewed U.S. Patent Application Serial No. 08/004,822. The application describes hydroxyl-substituted 3,4-diarylfurans (pages 2-3);

8. Based on my analysis, I believe one of ordinary skill in this art, including as it relates to tautomers, would understand that U.S. Patent Application No. 08/004,822 describes both the 3,4-diaryl-2-hydroxyfuran enol and carbonyl forms;

I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted

_____ _____

Date Victor Snieckus, Ph.D.

PATENT Case 5400/3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	
S. BERTENSHAW ET AL	GROUP ART UNIT: 120
SERIAL NO.: 08/425,029	EXAMINER: DENTZ
FILED: April 19, 1995	DATE: April 3, 1997

TITLE: A METHOD OF USING SUBSTITUTED FURANOL COMPOUNDS FOR THE TREATMENT OF CYCLOOXYGENASE-II ASSOCIATED DISORDERS

DECLARATION UNDER 37 C.F.R. §1.132

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Victor Snieckus, Ph.D., declare that:

1. I received a Bachelor of Science Degree in Chemistry from the University of Alberta in 1959; a Master of Science Degree from the University of California-Berkeley in 1961, and a Ph.D. in Chemistry from the University of Oregon in 1965;

2. Since 1967, I have been employed as a faculty member of the Department of Chemistry at the University of Waterloo, Waterloo, Ontario, Canada. Currently I hold the position of professor of Chemistry and I direct scientists carrying out research in organic chemistry synthetic methodology;

3. I am the principal author or co-author of approximately 180 publications, with several publications on organic chemistry synthesis methods, including methods and strategies of heteroaromatic metalation;

4. In my professional capacities, I closely and carefully follow the scientific literature regarding organic chemistry and specifically synthetic methods;

5. As a professor of chemistry at the University of Waterloo and an invited lecturer at universities and companies throughout the world, I am aware of what constitutes ordinary skill and knowledge in the art of heterocyclic chemistry. I have reviewed U.S. Patent Application Serial No. 08/004,822 (the "application"). Based on my review I understand the following facts as shown in Appendix "A":

a. the application fully describes the preparation of mixed 3,4-diaryl-2,5-furyl carboxylic methyl ester/acids **A** as the initial step in Generic Scheme 1, as illustrated on page 13 and described in the accompanying text;

b. one can readily prepare 3,4-diaryl-furan-2-carboxylic acids **B** from the mixed 3,4-diaryl-2,5-furyl carboxylic methyl ester/acids **A** with the decarboxylation and saponification steps described in the application;

c. one can readily prepare 3,4-diaryl-5-hydroxyfuran-2-carboxylic acids **C** following the three step method of Hörnfeldt [svensk kemisk tidskrift, 80, 343, 344 (1968)] where the 3,4-diaryl-furan-2-carboxylic acids **B** are treated with alkyllithium to form the furyllithium, conversion of the furyllithium to the boronic acid ester, followed by oxidation of the boronic acid ester with hydrogen peroxide to form the 5-hydroxyfuran **C**;

d. at the time of filing the application, it was well known that the 3,4-diaryl-5-hydroxyfuran-2-carboxylic acids **C** decarboxylate via the method of Rio and Serkiz [Bull. Soc. Chim. France, 1491-1495 (1976)] to form the corresponding 3,4-diaryl-2-hydroxyfuran anions **D** which are isolated as the carbonyl tautomers **E**;

6. Based on my analysis, I find that U.S. Patent Application No. 08/004,822, in light of the art existing at the

time of filing this patent application, teaches how to prepare the 3,4-diphenyl-2-hydroxyfurans, and the tautomers thereof.

I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted

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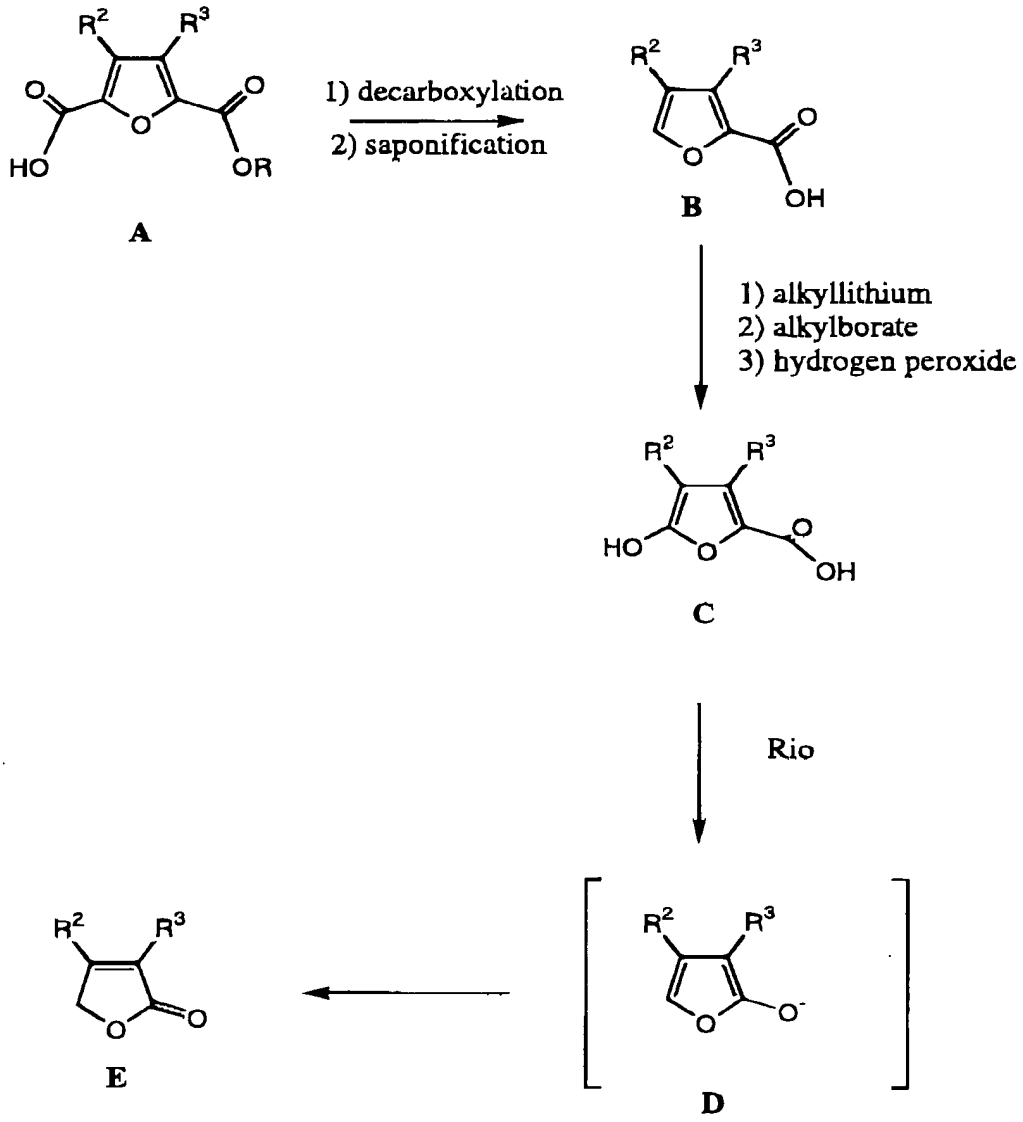
Date Victor Snieckus, Ph.D.

APPENDIX A


R2
R3
O
O
HO
OR
A
1) decarboxylation
2) saponification
B
OH
1) alkyllithium
2) alkylborate
3) hydrogen peroxide
C
HO
Rio
D
O-
E

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DECLARATION UNDER 37 C.F.R. §1.132

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Richard B. Silverman, Ph.D., declare that:

1. I received a Bachelor of Science Degree in Chemistry from Pennsylvania State University, in 1968; and received a Ph.D. in Chemistry from Harvard University in 1974;

2. Since 1976, I have been employed as a faculty member of the Chemistry Department at Northwestern University, Evanston, Illinois, and that currently I hold the position of Arthur Andersen Teaching and Research Professor of Chemistry and of Biochemistry, Molecular Biology and Cell Biology, with responsibility for scientists carrying out research in medicinal chemistry;

3. I am the principal author or co-author of approximately 150 publications and books, with several publications on organic chemistry synthesis methods, including the synthesis of dihydrofuranone compounds;

4. In my professional capacities, I closely and carefully follow the scientific literature regarding organic chemistry and specifically synthetic methods;

5. As a professor of chemistry at Northwestern University, with teaching responsibilities for undergraduate and graduate students, I am aware of what constitutes ordinary skill and knowledge in the art of heterocyclic chemistry. I have reviewed U.S. Patent Application Serial No. 08/004,822 (the "application"). Based on my review I understand the following facts as shown in Appendix "A":

a. the application fully describes the preparation of mixed 3,4-diaryl-2,5-furyl carboxylic methyl ester/acids **A** as the initial step in Generic Scheme 1, as illustrated on page 13 and described in the accompanying text;

b. one can readily prepare 3,4-diaryl-2-furyl carboxylic methyl ester **B** from the mixed 3,4-diaryl-2,5-furyl carboxylic methyl ester/acids **A** with the decarboxylation step described in the application;

c. one can readily prepare 3,4-diaryl-2-furfurals **C** from the 3,4-diaryl-2-furyl carboxylic methyl ester **B** by reducing the ester **B** with a borohydride to form a furyl-2-methanol, followed by Swern oxidation of the alcohol to form the aldehyde **C** [Omura and Swern, Tetrahedron, 34, 1651 (1978)];

d. alternatively, one can readily prepare 3,4-diaryl-2-furfurals **C** from the 3,4-diaryl-2-furans **D** (prepared as described in the application) via the Vilsmeier-Haack reaction [Ber., 60, 119 (1927)];

e. the 3,4-diaryl-2-furfurals **C** are oxidized via the Baeyer-Villiger method [see Chem. Abstr., 90, 54751x (1979)] to form the 3,4-diaryl-2-furyl formate esters **E**, and the 3,4-diaryl-2-hydroxyfuran anions **F** which are isolated as the carbonyl tautomers **G**;

6. Based on my analysis, I find that U.S. Patent Application No. 08/004,822, in light of the art existing at the time of filing this patent application, teaches how to prepare the 3,4-diphenyl-2-hydroxyfurans, and the tautomers thereof.

I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Respectfully submitted

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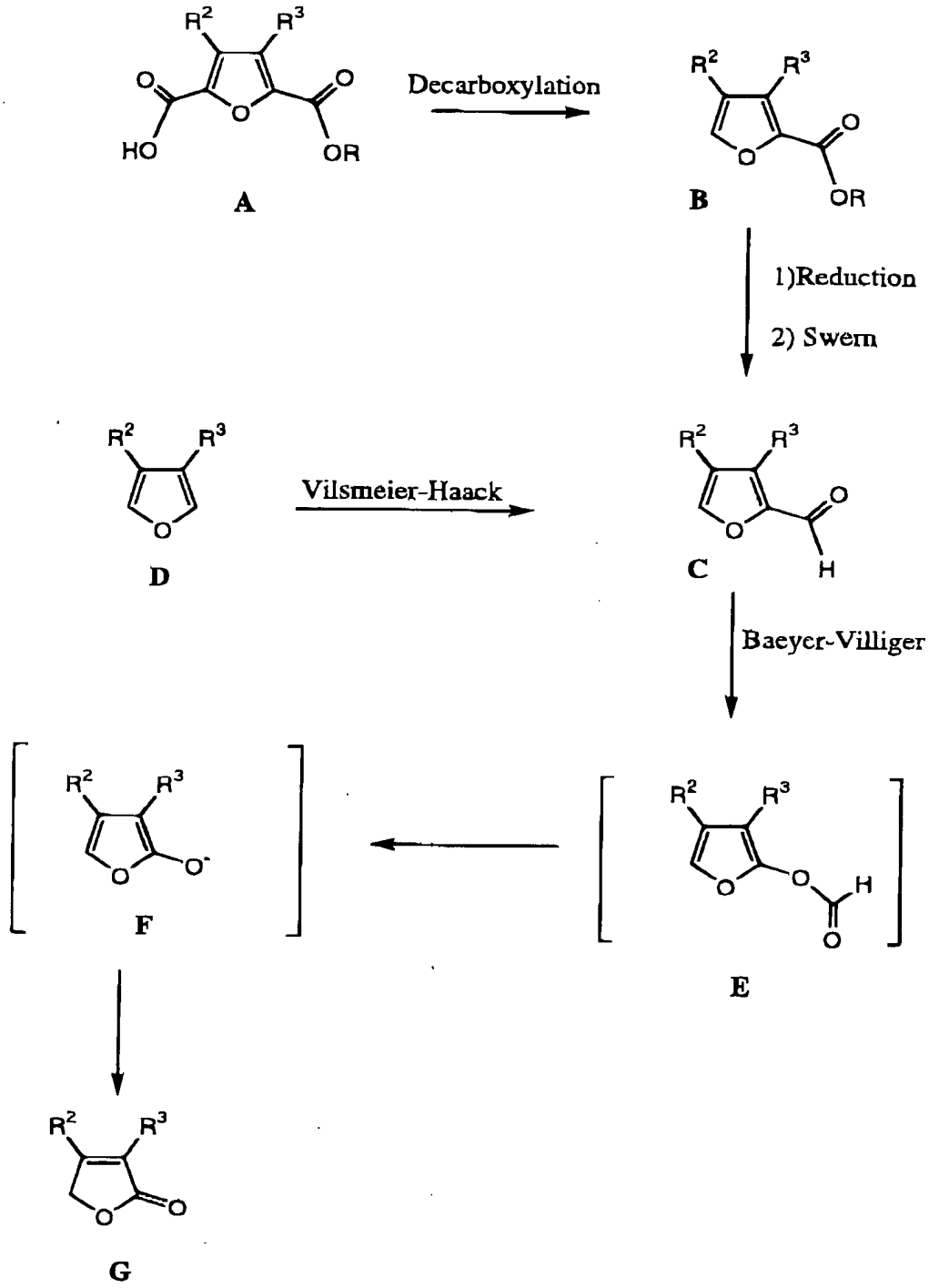
Date Richard B. Silverman, Ph.D.

APPENDIX A


R2
R3
O
HO
OR
Decarboxylation
A
B
1)Reduction
2) Swern
D
Vilsmeier-Haack
C
H
Baeyer-Villiger
F
E
G